

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use NovoSeven RT safely and effectively. See full prescribing information for NovoSeven RT.

**NovoSeven® RT, Coagulation Factor VIIa (Recombinant)  
For Intravenous Use Only. Lyophilized Powder for Solution for Injection  
Initial U.S. Approval: 1999**

**WARNING: THROMBOSIS**

See full prescribing information for complete boxed warning

- Serious arterial and venous thrombotic events following administration of NovoSeven RT have been reported.
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven RT.
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis (5.1).

**RECENT MAJOR CHANGES**

Boxed Warning	07/2014
Indications and Usage, Glanzmann’s thrombasthenia (1)	07/2014
Dosage and Administration, Glanzmann’s thrombasthenia (2.1)	07/2014
Administration (2.3)	04/2014
Warnings and Precautions (5.1, 5.2)	07/2014

**INDICATIONS AND USAGE**

NovoSeven RT (Coagulation Factor VIIa [Recombinant]) is a coagulation factor indicated for:

- Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann’s thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets (1)
- Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia (1)

**DOSAGE AND ADMINISTRATION**

**For intravenous bolus injection only**

- Administer NovoSeven RT to patients only under the supervision of a physician experienced in the treatment of bleeding disorders (2.1)
- After reconstitution, administer within 3 hours; do not freeze or store in syringes (2.3)

**Bleeding Episodes (2.1)**

Indication	Dosing Recommendation
Congenital Hemophilia A or B with Inhibitors	<ul style="list-style-type: none"> <li>• 90 mcg/kg every 2 hours, adjustable based on severity of bleeding until hemostasis is achieved</li> <li>• 90 mcg/kg every 3-6 hours after hemostasis is achieved for severe bleeds</li> </ul>
Acquired Hemophilia	<ul style="list-style-type: none"> <li>• 70-90 mcg/kg every 2-3 hours until hemostasis is achieved</li> </ul>
Congenital Factor VII Deficiency	<ul style="list-style-type: none"> <li>• 15-30 mcg/kg every 4-6 hours until hemostasis is achieved</li> </ul>
Glanzmann’s Thrombasthenia	<ul style="list-style-type: none"> <li>• 90 mcg/kg every 2-6 hours until hemostasis is achieved</li> </ul>

**Peri-operative Management (2.1)**

Indication	Dosing Recommendation
Congenital Hemophilia A or B with Inhibitors	<b>Minor:</b> <ul style="list-style-type: none"> <li>• 90 mcg/kg immediately before surgery, repeat every 2 hours during</li> </ul>

	surgery <ul style="list-style-type: none"> <li>• 90 mcg/kg every 2 hours after surgery for 48 hours, then every 2-6 hours until healing has occurred</li> </ul> <b>Major:</b> <ul style="list-style-type: none"> <li>• 90 mcg/kg immediately before surgery, repeat every 2 hours during surgery</li> <li>• 90 mcg/kg every 2 hours after surgery for 5 days, then every 4 hours until healing has occurred</li> </ul>
Acquired Hemophilia	<ul style="list-style-type: none"> <li>• 70-90 mcg/kg immediately before surgery and every 2-3 hours for the duration of surgery and until hemostasis is achieved</li> </ul>
Congenital Factor VII Deficiency	<ul style="list-style-type: none"> <li>• 15-30 mcg/kg immediately before surgery and every 4-6 hours for the duration of surgery and until hemostasis is achieved</li> </ul>
Glanzmann’s Thrombasthenia	<ul style="list-style-type: none"> <li>• 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure</li> <li>• 90 mcg/kg every 2-6 hours to prevent post-operative bleeding</li> </ul>

**DOSAGE FORMS AND STRENGTHS**

Available as lyophilized powder in single-use vials of 1, 2, 5, or 8 mg recombinant coagulation factor VIIa (FVIIa). After reconstitution with specified volume of histidine diluent, the final solution contains 1 mg per mL (1000 micrograms per mL) of recombinant FVIIa (3)

**CONTRAINDICATIONS**

None known (4)

**WARNINGS AND PRECAUTIONS**

- Serious arterial and venous thrombotic events may occur (5.1)
- Hypersensitivity reactions have been reported with NovoSeven RT. Anaphylaxis and other hypersensitivity reactions may occur. Should symptoms occur, discontinue NovoSeven RT and administer appropriate treatment (5.2)
- Monitor Factor VII deficient patients for prothrombin time (PT) and FVII coagulant activity, and for antibody formation to NovoSeven RT (5.3)

**ADVERSE REACTIONS**

The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven in clinical trials occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia (6)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1-877-668-6777 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

- Avoid simultaneous use of NovoSeven RT and aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) (7)
- Do not mix with other infusion solutions (7)
- Do not administer NovoSeven RT with coagulation factor XIII (FXIII) (7)

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: No human or animal data. Use only if clearly needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2014

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## FULL PRESCRIBING INFORMATION

### WARNING: THROMBOSIS

- Serious arterial and venous thrombotic events following administration of NovoSeven RT have been reported.
- Discuss the risks and explain the signs and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven RT.
- Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis. [See *Warnings and Precautions (5.1)*]

## 1 INDICATIONS AND USAGE

NovoSeven RT (Coagulation Factor VIIa [Recombinant]) is a coagulation factor indicated for:

- Treatment of bleeding episodes and peri-operative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets
- Treatment of bleeding episodes and peri-operative management in adults with acquired hemophilia

## 2 DOSAGE AND ADMINISTRATION

### For intravenous bolus administration only

#### 2.1 Dose

- Initiate treatment with NovoSeven RT under the supervision of a qualified healthcare professional experienced in the treatment of bleeding disorders.
- Use hemostasis evaluation to determine the effectiveness of NovoSeven RT and to provide a basis for modification of the NovoSeven RT treatment schedule.
- Coagulation parameters do not necessarily correlate with or predict the effectiveness of NovoSeven RT.

#### *Treatment of Acute Bleeding Episodes*

NovoSeven RT dosing for the treatment of acute bleeding episodes is provided in Table 1.

**Table 1: Dosing for Treatment of Acute Bleeding Episodes**

Dose* and Frequency	Duration of Therapy	Additional Information
<b>Congenital Hemophilia A or B with Inhibitors</b>		
<b>Hemostatic</b> 90 mcg/kg every two hours, adjustable based on severity of bleeding	Until hemostasis is achieved, or until the treatment has been judged to be inadequate	
<b>Post-Hemostatic</b> 90 mcg/kg every 3-6 hours for severe bleeds	After hemostasis is achieved to maintain the hemostatic plug	The appropriate duration of post-hemostatic dosing has not been studied
<b>Acquired Hemophilia</b>		
70-90 mcg/kg every 2-3 hours	Until hemostasis is achieved	
<b>Congenital Factor VII Deficiency</b>		
15-30 mcg/kg every 4-6 hours	Until hemostasis is achieved	Effective treatment has been achieved with doses as low as 10 micrograms per kg body weight. Adjust dose and frequency of injections to each individual patient
<b>Glanzmann's Thrombasthenia</b>		
90 mcg/kg every 2-6 hours	In severe bleeding episodes requiring systemic hemostatic therapy until hemostasis is achieved	Platelet transfusions are the primary treatment in patients with Glanzmann's Thrombasthenia without refractoriness to platelets or in patients without platelet-specific antibodies

\* The minimum effective dose has not been determined

#### Congenital Hemophilia A or B with inhibitors

- Dose and administration interval may be adjusted to the individual patient based on the severity of the bleeding.<sup>1</sup>
- For patients treated for joint or muscle bleeds, a decision on outcome was reached for a majority of patients within eight doses although more doses were required for severe bleeds. A majority of patients who reported adverse experiences received more than twelve doses. Monitor and minimize the duration of any post-hemostatic dosing.

#### *Perioperative Management*

NovoSeven RT dosing for prevention of bleeding in surgical interventions or invasive procedures (perioperative management) is provided in Table 2.

**Table 2: Dosing for Perioperative Management**

Type of Surgery	Dose and Frequency	Additional Information
<b>Congenital Hemophilia A or B with Inhibitors</b>		
<b>Minor</b>	<p><b>Initial:</b> 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery</p> <p><b>Post surgical:</b> 90 mcg/kg every 2 hours for 48 hours then every 2-6 hours until healing occurs</p>	
<b>Major</b>	<p><b>Initial:</b> 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the surgery</p> <p><b>Post surgical:</b> 90 mcg/kg every 2 hours for 5 days then every 4 hours until healing occurs</p>	Additional bolus doses should be administered if required
<b>Acquired Hemophilia</b>		
<b>Minor or Major</b>	70-90 mcg/kg immediately before surgery and repeat every 2-3 hours for the duration of the surgery and until hemostasis is achieved*	
<b>Congenital Factor VII Deficiency</b>		
<b>Minor or Major</b>	<p>15-30 mcg/kg immediately before surgery and repeat every 4-6 hours for the duration of the surgery and until hemostasis is achieved*</p> <p>Adjust dose and frequency of injections to each individual patient</p>	Effective treatment has been achieved with doses as low as 10 micrograms per kg body weight
<b>Glanzmann's Thrombasthenia</b>		
<b>Minor or Major</b>	<p><b>Initial:</b> 90 mcg/kg immediately before surgery and repeat every 2 hours for the duration of the procedure*</p> <p><b>Post surgical:</b> 90 mcg/kg every 2-6 hours to prevent post-operative bleeding*</p>	Higher average infused doses (median dose was 100 micrograms per kg (IQR 90-140)) were noted for surgical patients who had clinical refractoriness with or without platelet-specific antibodies compared to those with neither

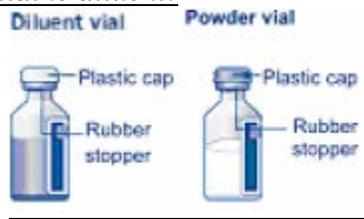
\*The minimum effective dose has not been determined.

## 2.2 Reconstitution

- Follow the procedures below for the preparation and reconstitution of NovoSeven RT. For questions regarding reconstitution, please contact Novo Nordisk at 1-877-NOVO-777.
- Calculate the NovoSeven RT dosage and select the appropriate NovoSeven RT package provided with either 1 histidine diluent vial or 1 pre-filled histidine diluent syringe.

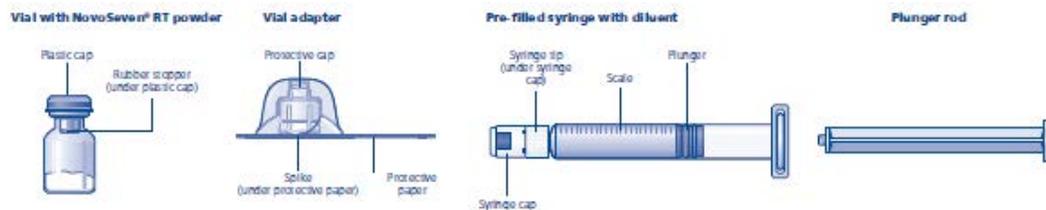
- Reconstitute only with the histidine diluent provided with NovoSeven RT.

NovoSeven RT package containing 1 vial of NovoSeven RT powder and 1 vial of histidine diluent:



1. Always use aseptic technique.
2. Bring NovoSeven RT (white, lyophilized powder) and the specified volume of histidine (diluent) to room temperature, but not above 37°C (98.6° F). The specified volume of diluent corresponding to the amount of NovoSeven RT is as follows:
  - 1 mg (1000 micrograms) vial + 1.1 mL Histidine diluent
  - 2 mg (2000 micrograms) vial + 2.1 mL Histidine diluent
  - 5 mg (5000 micrograms) vial + 5.2 mL Histidine diluent
  - 8 mg (8000 micrograms) vial + 8.1 mL Histidine diluent
3. Remove caps from the NovoSeven RT vials to expose the central portion of the rubber stopper. Cleanse the rubber stoppers with an alcohol swab and allow to dry prior to use.
4. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe. It is recommended to use syringe needles of gauge size 20-26.
5. Insert the needle of the syringe into the Histidine diluent vial. Inject air into the vial and withdraw the quantity required for reconstitution.
6. Insert the syringe needle containing the diluent into the NovoSeven RT vial through the center of the rubber stopper, aiming the needle against the side so that the stream of liquid runs down the vial wall (the NovoSeven RT vial does not contain a vacuum). **Do not inject the diluent directly on the NovoSeven RT powder.**
7. Gently swirl the vial until all the material is dissolved. The reconstituted solution is a clear, colorless solution which may be stored either at room temperature or refrigerated for up to 3 hours after reconstitution. After reconstitution with the specified volume of diluent, each vial contains approximately 1 mg per mL NovoSeven RT (1000 micrograms per mL).

NovoSeven RT package containing 1 vial of NovoSeven RT powder and 1 pre-filled histidine diluent syringe with vial adapter for needleless reconstitution:



1. Always use aseptic technique.
2. Bring NovoSeven RT (white, lyophilized powder) and the specified volume of histidine (diluent) to room temperature, but not above 37°C ( 98.6° F). The specified volume of diluent corresponding to the amount of NovoSeven RT is as follows:  
1 mg (1000 micrograms) vial + 1 mL Histidine diluent in pre-filled syringe  
2 mg (2000 micrograms) vial + 2 mL Histidine diluent in pre-filled syringe  
5 mg (5000 micrograms) vial + 5 mL Histidine diluent in pre-filled syringe  
8 mg (8000 micrograms) vial + 8 mL Histidine diluent in pre-filled syringe
3. Remove cap from the NovoSeven RT vial. Cleanse the rubber stopper with an alcohol swab and allow to dry prior to use.
4. Peel back the protective paper from the vial adapter. Do not remove the vial adapter from the package.
5. Place the NovoSeven RT vial on a flat surface. While holding the vial adapter package, place the vial adapter over the NovoSeven RT vial and press down firmly on the package until the vial adapter spike penetrates the rubber stopper.
6. Attach the plunger rod to the syringe. Turn the plunger rod clockwise into the plunger inside the pre-filled diluent syringe until resistance is felt. Remove the syringe cap from the pre-filled diluent syringe and screw onto the vial adapter.
7. Push the plunger rod to slowly inject all the diluent into the vial. Keep the plunger rod pressed down and swirl the vial gently until the powder is dissolved. The reconstituted solution is a clear, colorless solution which may be stored fully assembled either at room temperature or refrigerated for up to 3 hours after reconstitution. After reconstitution with the specified volume of diluent, each vial contains approximately 1 mg per mL NovoSeven RT (1000 micrograms per mL).

### 2.3 Administration

#### For intravenous bolus injection only

- Inspect the reconstituted NovoSeven RT visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if particulate matter or discoloration is observed.
- Do not freeze reconstituted NovoSeven RT or store it in syringes.
- Administer within 3 hours after reconstitution.
- Do not mix with other infusion solutions.
- Discard any unused solution.

Perform the following procedures immediately prior to administration:

*NovoSeven RT package containing 1 vial of NovoSeven RT powder and 1 vial of histidine diluent:*

1. Always use aseptic technique.
2. Draw back the plunger of a sterile syringe (attached to sterile needle) and admit air into the syringe.
3. Insert needle into the vial of reconstituted NovoSeven RT. Inject air into the vial and then withdraw the appropriate amount of reconstituted NovoSeven RT into the syringe.
4. Remove and discard the needle from the syringe.

*NovoSeven RT package containing 1 vial of NovoSeven RT powder and 1 pre-filled histidine diluent syringe with vial adapter for needleless reconstitution:*

1. Always use aseptic technique.
2. Invert the NovoSeven RT vial. Stop pushing the plunger rod and let it move back on its own while the mixed solution fills the syringe. Pull the plunger rod slightly downwards to draw the mixed solution into the syringe. Tap the syringe to remove air bubbles and withdraw the required dose amount of reconstituted NovoSeven RT into the syringe.
3. Unscrew the vial adapter with the vial. Discard the empty NovoSeven RT vial with the vial adapter attached.

*Caution:*

- The pre-filled diluent syringe is made of glass with an internal tip diameter of 0.037 inches, and is compatible with a standard Luer-lock connector.
- Some needleless connectors for intravenous catheters are incompatible with the glass diluent syringes (for example, certain connectors with an internal spike, such as Clave<sup>®</sup> /MicroClave<sup>®</sup>, InVision-Plus<sup>®</sup>, InVision-Plus CS<sup>®</sup>, InVision-Plus<sup>®</sup> Junior<sup>®</sup>, Bionector<sup>®</sup>), and their use can damage the connector and affect administration. To administer product through incompatible needleless connectors, withdraw reconstituted product into a standard 10 mL sterile Luer-lock plastic syringe.
- If you have encountered any problems with attaching the pre-filled histidine diluent syringe to any Luer-lock compatible device, please contact Novo Nordisk at (877) 668-6777.

Administer NovoSeven RT using the following procedures:

1. Administer as a slow bolus injection over 2 to 5 minutes, depending on the dose administered.
2. If line needs to be flushed before or after NovoSeven RT administration, use 0.9% Sodium Chloride Injection, USP.
3. Discard any unused reconstituted NovoSeven RT after 3 hours.

### **3 DOSAGE FORMS AND STRENGTHS**

NovoSeven RT is available as a white lyophilized powder in single-use vials containing 1 mg (1000 micrograms), 2 mg (2000 micrograms), 5 mg (5000 micrograms), or 8 mg (8000 micrograms) recombinant coagulation Factor VIIa (rFVIIa) per vial.

The diluent for reconstitution of NovoSeven RT is a 10 mmol solution of L-histidine in water for injection. It is a clear colorless solution provided in a vial or a pre-filled diluent syringe and is referred to as the histidine diluent.

After reconstitution with the histidine diluent, the final solution contains approximately 1 mg per mL NovoSeven RT (1000 micrograms per mL).

### **4 CONTRAINDICATIONS**

None known.

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Thrombosis**

Serious arterial and venous thrombotic events have been reported in clinical trials and postmarketing surveillance.

Patients with disseminated intravascular coagulation (DIC), advanced atherosclerotic disease, crush injury, septicemia, or concomitant treatment with aPCCs/PCCs (activated or nonactivated prothrombin complex concentrates) and uncontrolled post-partum hemorrhage have an increased risk of developing thromboembolic events due to circulating tissue factor (TF) or predisposing coagulopathy [*See Adverse Reactions (6.1) and Drug Interactions (7)*].

Exercise caution when administering NovoSeven RT to patients with an increased risk of thromboembolic complications. These include, but are not limited to, patients with a history of coronary heart disease, liver disease, disseminated intravascular coagulation, post-operative immobilization, elderly patients and neonates. In each of these situations, the potential benefit of treatment with NovoSeven RT should be weighed against the risk of these complications.

Monitor patients who receive NovoSeven RT for development of signs or symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical

thrombosis, reduce the dose of NovoSeven RT or stop the treatment, depending on the patient's condition.

## **5.2 Hypersensitivity Reactions**

Hypersensitivity reactions, including anaphylaxis have been reported with NovoSeven RT. Administer NovoSeven RT only if clearly needed in patients with known hypersensitivity to NovoSeven RT or any of its components, or in patients with known hypersensitivity to mouse, hamster, or bovine proteins. Should symptoms occur, discontinue NovoSeven RT, administer appropriate treatment and weigh the benefit/risks prior to restarting treatment with NovoSeven RT.

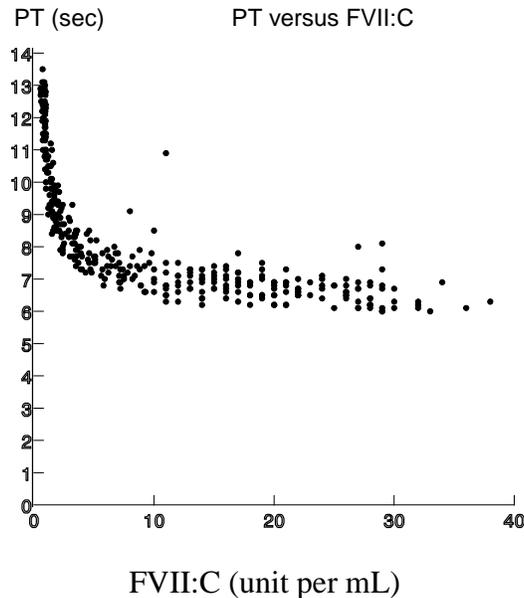
## **5.3 Antibody Formation in Factor VII Deficient Patients**

Factor VII deficient patients should be monitored for prothrombin time (PT) and factor VII coagulant activity before and after administration of NovoSeven RT. If the factor VIIa activity fails to reach the expected level, or prothrombin time is not corrected, or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed.

## **5.4 Laboratory Tests**

Laboratory coagulation parameters (PT/INR, aPTT, FVII:C) have shown no direct correlation to achieving hemostasis. Assays of prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), and plasma FVII clotting activity (FVII:C), may give different results with different reagents. Treatment with NovoSeven has been shown to produce the following characteristics:

PT: As shown below, in patients with hemophilia A/B with inhibitors, the PT shortened to about a 7-second plateau at a FVII:C level of approximately 5 units per mL. For FVII:C levels > 5 units per mL, there is no further change in PT. The clinical relevance of prothrombin time shortening following NovoSeven RT administration is unknown.



**INR:** NovoSeven has demonstrated the ability to normalize INR. However, INR values have not been shown to directly predict bleeding outcomes, nor has it been possible to demonstrate the impact of NovoSeven on bleeding times/volume in models of clinically-induced bleeding in healthy volunteers who had received Warfarin, when laboratory parameters (PT/INR, aPTT, thromboelastogram) have normalized.

**aPTT:** While administration of NovoSeven shortens the prolonged aPTT in hemophilia A/B patients with inhibitors, normalization has usually not been observed in doses shown to induce clinical improvement. Data indicate that clinical improvement was associated with a shortening of aPTT of 15 to 20 seconds.

**FVIIa:C:** FVIIa:C levels were measured two hours after NovoSeven administration of 35 micrograms per kg body weight and 90 micrograms per kg body weight following two days of dosing at two hour intervals. Average steady state levels were 11 and 28 units per mL for the two dose levels, respectively.

## 6 ADVERSE REACTIONS

The most common and serious adverse reactions in clinical trials are thrombotic events. Thrombotic adverse reactions following the administration of NovoSeven in clinical trials

occurred in 4% of patients with acquired hemophilia and 0.2% of bleeding episodes in patients with congenital hemophilia.

## 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in clinical trials of another drug, and may not reflect rates observed in practice.

Adverse reactions outlined below have been reported from clinical trials and data collected in registries.

### *Hemophilia A or B Patients with Inhibitors*

In two studies for hemophilia A or B patients with inhibitors treated for bleeding episodes (N=298), adverse reactions were reported in  $\geq 2\%$  of the patients that were treated with NovoSeven for 1,939 bleeding episodes (see Table 3 below).

**Table 3: Adverse Reactions Reported in  $\geq 2\%$  of the 298 Patients with Hemophilia A or B with Inhibitors**

<b>Body System Reactions</b>	<b># of adverse reactions (n=1,939 treatments)</b>	<b># of patients (n=298 patients)</b>
<b>Body as a whole</b>		
Fever	16	13
<b>Platelets, Bleeding, and Clotting</b>		
Fibrinogen plasma decreased	10	5
<b>Cardiovascular</b>		
Hypertension	9	6

Serious adverse reactions included thrombosis, pain, thrombophlebitis deep, pulmonary embolism, decreased therapeutic response, cerebrovascular disorder, angina pectoris, DIC, anaphylactic shock and abnormal hepatic function. The serious adverse reactions of DIC and therapeutic response decreased had a fatal outcome.

There have been no confirmed reports of inhibitory antibodies against NovoSeven or FVII in patients with congenital hemophilia A or B with alloantibodies.

In two clinical trials evaluating safety and efficacy of NovoSeven administration in the peri-operative setting in hemophilia A or B patients with inhibitors (N=51), the following serious adverse reactions were reported: acute post-operative hemarthrosis (n=1), internal jugular thrombosis adverse reaction (n=1), decreased therapeutic response (n=4)

### *Congenital Factor VII Deficiency*

Data collected from the compassionate/emergency use programs, the published literature, a pharmacokinetics study, and the Hemophilia and Thrombosis Research Society<sup>2</sup> (HTRS) registry showed that 75 patients with Factor VII deficiency had received NovoSeven: 70 patients for 124 bleeding episodes, surgeries, or prophylaxis; 5 patients in the pharmacokinetics trial. The following adverse reactions were reported: intracranial hypertension (n=1), IgG antibody against rFVIIa and FVII (n=1), localized phlebitis (n=1).

As with all therapeutic proteins, there is a potential for immunogenicity. Patients with factor VII deficiency treated with NovoSeven RT should be monitored for factor VII antibodies. The incidence of antibody formation is dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to NovoSeven RT with the incidence of antibodies to other products may be misleading.

#### Acquired Hemophilia

Data collected from four compassionate use programs, the HTRS registry, and the published literature showed that 139 patients with acquired hemophilia received NovoSeven for 204 bleeding episodes, surgeries and traumatic injuries. Of these 139 patients, 6 patients experienced 8 serious adverse reactions. Serious adverse reactions included shock (n=1), cerebrovascular accident (n=1) and thromboembolic events (n=6) which included cerebral artery occlusion, cerebral ischemia, angina pectoris, myocardial infarction, pulmonary embolism and deep vein thrombosis. Three of the serious adverse reactions had a fatal outcome.

#### Glanzmann's Thrombasthenia

Data collected from the Glanzmann's Thrombasthenia Registry (GTR) and the HTRS registry showed that 140 patients with Glanzmann's thrombasthenia received NovoSeven RT for 518 bleeding episodes, surgeries or traumatic injuries. The following adverse reactions were reported: deep vein thrombosis (n=1), headache (n=2), fever (n=2), nausea (n=1), and dyspnea (n=1).

## **6.2 Postmarketing Experience**

The following adverse reactions have been identified during post approval use of NovoSeven. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

**Table 4: Post Marketing Experience**

<b>MedDRA System Organ Class</b>	<b>Preferred Term</b>
Immune system disorders	Hypersensitivity (including anaphylactic shock, flushing, urticaria, rash, angioedema)
Vascular disorders	Thromboembolic events (including hepatic artery thrombosis, myocardial infarction, cerebral infarction, intestinal infarction, intracardiac thrombus, peripheral ischemia, portal vein thrombosis, myocardial ischemia, renal artery thrombosis)

## 7 DRUG INTERACTIONS

- Avoid simultaneous use of activated prothrombin complex concentrates or prothrombin complex concentrates. The risk of a potential interaction between NovoSeven RT and coagulation factor concentrates has not been adequately evaluated in preclinical or clinical studies.
- Do not mix NovoSeven RT with infusion solutions.
- Thrombosis may occur if NovoSeven RT is administered concomitantly with Coagulation Factor XIII. [See *Nonclinical Toxicology (13.2)*]

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. NovoSeven RT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Treatment of rats and rabbits with NovoSeven in reproduction studies has been associated with mortality at doses up to 6 mg per kg body weight and 5 mg per kg body weight respectively. At 6 mg per kg body weight in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg per kg body weight, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg per kg body weight of NovoSeven gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven.

### 8.2 Labor and Delivery

There are no adequate and well-controlled studies in labor, delivery, and postpartum periods. NovoSeven RT has caused thrombosis when used to control post-partum hemorrhage.

### **8.3 Nursing Mothers**

It is not known whether NovoSeven RT is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### **8.4 Pediatric Use**

Clinical trials enrolling pediatric patients were conducted with dosing determined according to body weight and not according to age. The safety and effectiveness of NovoSeven RT has not been studied to determine if there are differences among various age groups, from infants to adolescents (0 to 16 years of age).

In the Glanzmann's Thrombasthenia Registry, NovoSeven was used in 43 children aged 0-12 years for 157 bleeding episodes and in 15 children aged 0-12 years for 19 surgical procedures. NovoSeven also was used in 8 children aged >12 to 16 years for 17 bleeding episodes and in 3 children aged >12 to 16 years for 3 surgical procedures. Efficacy of regimens including NovoSeven was evaluated by independent adjudicators as 93.6% and 100% for bleeding episodes in children aged 0-12 years and >12-16 years, respectively. Efficacy in surgical procedures was evaluated as 100% for all surgical procedures in children aged 0-16 years. No adverse reactions were reported in children.

### **8.5 Geriatric Use**

Clinical studies of NovoSeven RT in congenital factor deficiencies and Glanzmann's thrombasthenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

## **10 OVERDOSAGE**

Dose limiting toxicities of NovoSeven RT have not been investigated in clinical trials. The following are examples of accidental overdose.

- One newborn female with congenital factor VII deficiency was administered an overdose of NovoSeven (single dose: 800 micrograms per kg body weight). Following additional administration of NovoSeven and various plasma products, antibodies against rFVIIa were detected, but no thrombotic complications were reported.
- One Factor VII deficient male (83 years of age, 111.1 kg) received two doses of 324 micrograms per kg body weight (10-20 times the recommended dose) and experienced a thrombotic event (occipital stroke).
- One hemophilia B patient (16 years of age, 68 kg) received a single dose of 352 micrograms per kg body weight and one hemophilia A patient (2 years of age, 14.6 kg) received doses ranging from 246 micrograms per kg body weight to 986 micrograms per kg body weight on five consecutive days. There were no reported complications in either case.

## 11 DESCRIPTION

NovoSeven RT is recombinant human coagulation Factor VIIa (rFVIIa), intended for promoting hemostasis by activating the extrinsic pathway of the coagulation cascade.<sup>3</sup> NovoSeven RT is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues (MW 50 K Dalton). NovoSeven RT is structurally similar to human plasma-derived Factor VIIa.

The gene for human Factor VII is cloned and expressed in baby hamster kidney cells (BHK cells). Recombinant FVII is secreted into the culture media (containing newborn calf serum) in its single-chain form and then proteolytically converted by autocatalysis to the active two-chain form, rFVIIa, during a chromatographic purification process. The purification process has been demonstrated to remove exogenous viruses (MuLV, SV40, Pox virus, Reovirus, BEV, IBR virus). No human serum or other proteins are used in the production or formulation of NovoSeven RT.

NovoSeven RT is supplied as a sterile, white lyophilized powder of rFVIIa in single-use vials. Each vial of lyophilized drug contains the following:

<b>Contents</b>	<b>1 mg Vial</b>	<b>2 mg Vial</b>	<b>5 mg Vial</b>	<b>8 mg Vial</b>
rFVIIa	1000	2000	5000	8000
	micrograms	micrograms	micrograms	micrograms
sodium chloride*	2.34 mg	4.68 mg	11.7 mg	18.72 mg
calcium chloride dihydrate*	1.47 mg	2.94 mg	7.35 mg	11.76 mg
Glycylglycine	1.32 mg	2.64 mg	6.60 mg	10.56 mg
polysorbate 80	0.07 mg	0.14 mg	0.35 mg	0.56 mg
Mannitol	25 mg	50 mg	125 mg	200 mg
Sucrose	10 mg	20 mg	50 mg	80 mg
Methionine	0.5 mg	1.0 mg	2.5 mg	4 mg

\* per mg of rFVIIa: 0.4 mEq sodium, 0.01 mEq calcium

The diluent for reconstitution of NovoSeven RT is a 10 mmol solution of histidine in water for injection and is supplied as a clear colorless solution in a vial or pre-filled diluent syringe.

After reconstitution with the appropriate volume of histidine diluent, each vial contains approximately 1 mg/mL NovoSeven RT (corresponding to 1000 micrograms/mL). The reconstituted vials have a pH of approximately 6.0.

The reconstituted product is a clear colorless solution which contains no preservatives. NovoSeven RT contains trace amounts of proteins derived from the manufacturing and purification processes such as mouse IgG (maximum of 1.2 ng/mg), bovine IgG

(maximum of 30 ng/mg), and protein from BHK-cells and media (maximum of 19 ng/mg).

## **12 CLINICAL PHARMACOLOGY**

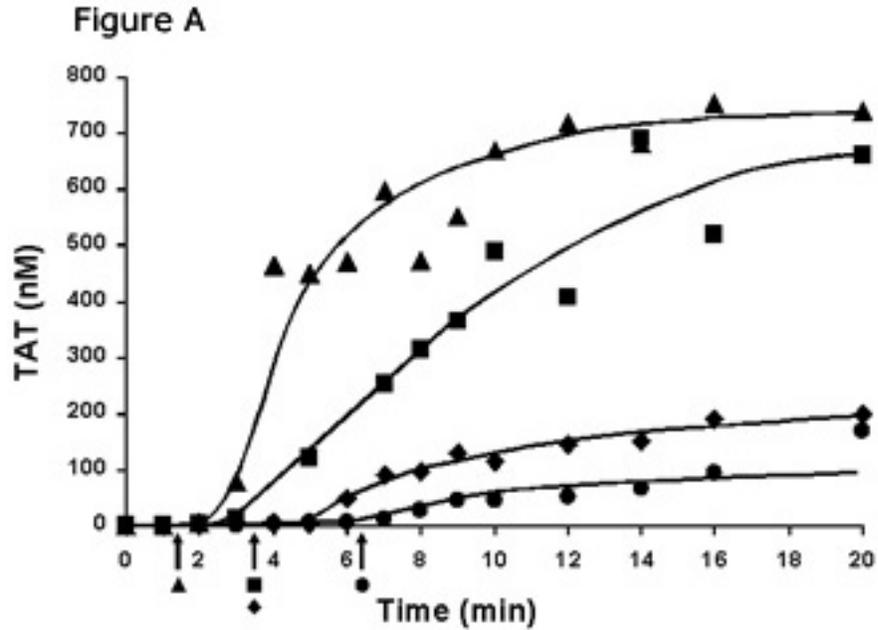
### **12.1 Mechanism of Action**

NovoSeven RT is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. This process may also occur on the surface of activated platelets.

### **12.2 Pharmacodynamics**

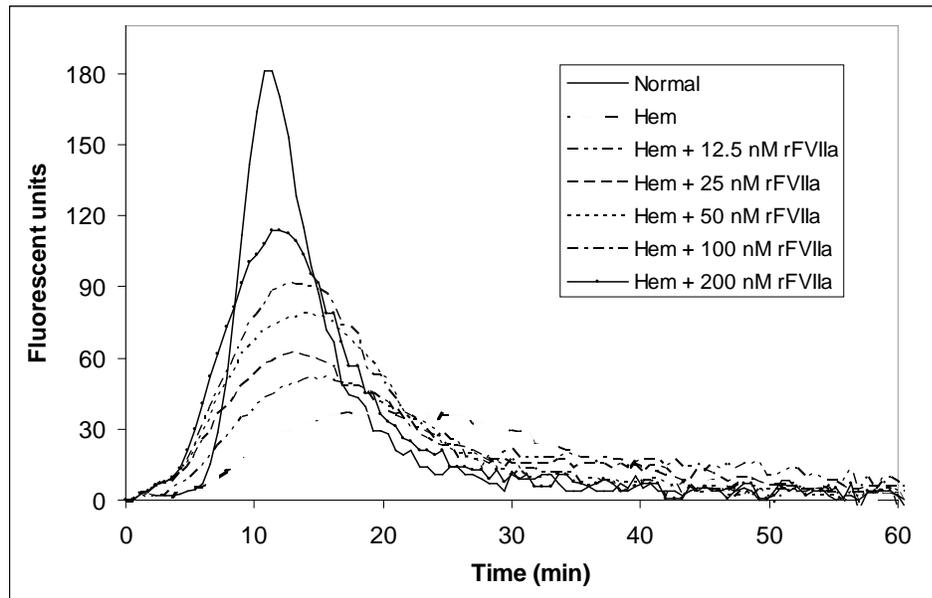
The effect of NovoSeven RT upon coagulation in patients with or without hemophilia has been assessed in different model systems. In an *in vitro* model of tissue-factor-initiated blood coagulation (Figure A),<sup>4</sup> the addition of rFVIIa increased both the rate and level of thrombin generation in normal and hemophilia A blood, with an effect shown at rFVIIa concentrations as low as 10 nM. In this model, fresh human blood was treated with corn trypsin inhibitor (CTI) to block the contact pathway of blood coagulation. Tissue factor (TF) was added to initiate clotting in the presence and absence of rFVIIa for both types of blood.

In a separate model, and in line with previous reports,<sup>5</sup> escalating doses of rFVIIa in hemophilia plasma demonstrate a dose-dependent increase in thrombin generation (Figure B). In this model, platelet rich normal and hemophilia plasma was adjusted with autologous plasma to 200,000 platelets/microliter. Coagulation was initiated by addition of tissue factor and CaCl<sub>2</sub>. Thrombin generation was measured in the presence of a thrombin substrate and various added concentrations of rFVIIa.



**TF-initiated clotting of normal blood and congenital hemophilia A blood in the presence of factor VIIa.** Clotting of CTI-inhibited (0.1 mg/mL) normal blood initiated with 12.5 pM TF (■) and addition of 10 nM factor VIIa (▲) and of hemophilia A blood with (◆) and without (●) addition of 10 nM factor VIIa. Figure A shows Thrombin Anti-Thrombin generation over time. Arrows indicate clotting times.

**Figure B**



**TF-initiated clotting of normal and hemophilia A platelet rich plasma in the presence of rFVIIa.**

## 12.3 Pharmacokinetics

### Healthy Subjects

The pharmacokinetics of NovoSeven was investigated in 35 healthy Caucasian and Japanese subjects in a dose-escalation study. Subjects were stratified according to gender and ethnic group and dosed with 40, 80 and 160 micrograms per kg NovoSeven.<sup>6</sup> Range of mean results across dose groups and ethnicity (Caucasian, Japanese) are shown in Table 5.

The products NovoSeven<sup>®</sup> and NovoSeven<sup>®</sup> RT are pharmacokinetically equivalent in a study of 22 patients receiving single doses of both formulations.<sup>7</sup> Mean results are shown in Table 5.

### Hemophilia A or B

Single dose pharmacokinetics of NovoSeven (17.5, 35, and 70 micrograms per kg) exhibited dose-proportional behavior in 15 subjects with hemophilia A or B in non-bleeding and bleeding state.<sup>8</sup> Median results (non-bleeding state) are shown in Table 5. Incremental recovery was 45.63%. In a bolus single-dose pharmacokinetic study, 5 male adults (90 micrograms per kg) and 10 male pediatric (2-12 years) patients (crossover, 90 and 180 micrograms per kg) with severe hemophilia A (10 of 18 subjects had inhibitors) received NovoSeven.<sup>9</sup> The PK of rFVII following 90 and 180 micrograms per kg IV dose in children indicated dose linearity. Results are shown in Table 5.

### Congenital Factor VII deficiency

Single dose pharmacokinetics of NovoSeven in 5 patients with severe congenital Factor VII deficiency (<1%), at doses of 15 and 30 micrograms per kg body weight, showed no significant difference between the two doses used with regard to dose-independent parameters. Mean results for the two doses (15, 30) are shown in Table 5. Incremental recovery was 18.9% (0.44 U/dl/U/kg) and 22.2% (0.51 U/dl/U/kg) with 15 and 30 micrograms per kg doses. No adverse reactions were reported in the pharmacokinetics for congenital factor VII deficiency.

The normal Factor VII plasma concentration is 0.5 micrograms per mL. Factor VII levels of 15-25% (0.075 – 0.125 micrograms per mL) are generally sufficient to achieve normal hemostasis.<sup>10</sup> For example, a 70 kg individual with FVII deficiency (plasma volume of approximately 3000 mL) would thus require 3.2 - 5.4 micrograms per kg of NovoSeven RT to secure hemostasis, assuming 100% recovery but, since the mean plasma recovery for NovoSeven is 20% for FVII-deficient patients, a NovoSeven RT dose range of 16-27 micrograms per kg

would be required to achieve sufficient FVII plasma levels for hemostasis, which is consistent with the recommended dose range.

**Table 5: Single Dose Pharmacokinetic Parameters**

Formulation (n)	Healthy Subjects			Hemophilia A or B			FVII Deficiency <sup>11</sup>
	rFVIIa (n=35) <sup>6</sup>	rFVIIa (n=22) <sup>7</sup>	rFVIIa-25C (n=22) <sup>7</sup>	rFVIIa (n=15) <sup>8</sup>	rFVIIa (n=5) <sup>9</sup>	rFVIIa (n=10) <sup>9</sup>	rFVIIa (n=5) <sup>11</sup>
Ages	20-45	22-44	22-44	15-63	30-45	2-12	20-43
Doses (mcg/kg)	40, 80, 160	90	90	17.5, 35, 70	90	90*, 180	15, 30
CL (mL/h/kg)	33-37	37.63	40.43	31.00	39	58	70.8, 79.1
t <sub>1/2</sub> (h)	3.9-6.0	3.48	3.54	2.89	3.1	2.6	2.82, 3.11
V <sub>ss</sub> (mL/kg)	130-165	111.31	122.96	106.5	128	164	280, 290
MRT (h)	ND	2.97	3.05	3.44	3.3	2.8	3.80, 3.75

\*Based upon the 90 mcg/kg dose

AUC Area under the curve, CL Clearance, t<sub>1/2</sub> terminal half-life, V<sub>ss</sub> Volume of distribution at steady state, MRT mean residence time, ND not determined, rFVIIa (NovoSeven<sup>®</sup> original formulation), rFVIIa-25C (NovoSeven<sup>®</sup> RT)

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two mutagenicity studies have given no indication of carcinogenic potential for NovoSeven. The clastogenic activity of NovoSeven was evaluated in both *in vitro* studies (*i.e.*, cultured human lymphocytes) and *in vivo* studies (*i.e.*, mouse micronucleus test). Neither of these studies indicated clastogenic activity of NovoSeven. Other gene mutation studies have not been performed with NovoSeven RT (*e.g.*, Ames test). No chronic carcinogenicity studies have been performed with NovoSeven RT.

A reproductive study in male and female rats at dose levels up to 3.0 mg per kg per day had no effect on mating performance, fertility, or litter characteristics.

Treatment of rats and rabbits with NovoSeven in reproduction studies has been associated with mortality at doses up to 6 mg per kg and 5 mg per kg. At 6 mg per kg in rats, the abortion rate was 0 out of 25 litters; in rabbits at 5 mg per kg, the abortion rate was 2 out of 25 litters. Twenty-three out of 25 female rats given 6 mg per kg of NovoSeven gave birth successfully, however, two of the 23 litters died during the early period of lactation. No evidence of teratogenicity was observed after dosing with NovoSeven.

### 13.2 Animal Toxicology and/or Pharmacology

In a monkey cardiovascular safety pharmacology model evaluating the combination of excessive doses of Coagulation Factor XIII A-Subunit (Recombinant) (585 IU/kg, 17 times the expected human dose) in combination with rFVIIa (1000 mcg/kg, 11 times the expected human dose), one of the twelve monkeys died 4 hours after treatment due to thrombosis. Procoagulant risk factors, including 6 indwelling catheters per monkey and the induction of anesthesia, may have complicated the study results. It is unclear whether the

mortality was related to the overdose of one or both products, or a specific interaction between them. Nonclinical and clinical studies with the combination of rFXIII and NovoSeven RT at recommended human doses have not been performed.

## 14 CLINICAL STUDIES

### 14.1 Hemophilia A or B with Inhibitors

The largest number of patients (N=483) who received NovoSeven during the investigational phase of product development were in an open protocol study<sup>12,13,14</sup> that began enrollment in 1988, shortly after the completion of the pharmacokinetic study. These patients included persons with hemophilia types A or B (with or without inhibitors), persons with acquired inhibitors to Factor VIII or Factor IX, and a few FVII deficient patients. The clinical situations were diverse and included muscle/joint bleeds, mucocutaneous bleeds, surgical prophylaxis, intracerebral bleeds, and other emergent situations.

A double-blind, randomized comparison trial<sup>15</sup> of two dose levels of NovoSeven in the treatment of joint, muscle and mucocutaneous hemorrhages in hemophilia A and B patients with and without inhibitors was conducted in 78 patients who received NovoSeven in treatment centers within 4 to 18 hours after experiencing a bleed. Thirty-five patients were treated at the 35 micrograms per kg dose (59 joint, 15 muscle and 5 mucocutaneous bleeding episodes) and 43 patients were treated at the 70 micrograms per kg dose (85 joint and 14 muscle bleeding episodes). Dosing was repeated at 2.5 hour intervals but ranged up to four hours for some patients. Efficacy was assessed at  $12 \pm 2$  hours or at end of treatment, whichever occurred first. Based on a subjective evaluation by the investigator, the respective efficacy rates for the 35 and 70 micrograms per kg groups were: excellent (definite relief of pain/tenderness as reported by the patient and/or a measureable decrease of the size of the haemorrhage and/or arrest of bleeding within 8 hours) 59% and 60%, effective (definite relief of pain/tenderness as reported by the patient and/or a measureable decrease of the size of the haemorrhage and/or arrest of bleeding within 8-14 hours) 12% and 11%, and partially effective (definite relief of pain/tenderness as reported by the patient and/or a measureable decrease of the size of the haemorrhage and/or arrest of bleeding after 14 hours) 17% and 20%. The average number of injections required to achieve hemostasis was 2.8 and 3.2 for the 35 and 70 micrograms per kg groups, respectively.

Two clinical trials were conducted to evaluate the safety and efficacy of NovoSeven administration during and after surgery in hemophilia A or B patients with inhibitors. One of the studies was a randomized, double-blind, parallel group clinical trial (28 patients with hemophilia A or B and inhibitors and one patient with acquired inhibitor to FVIII, undergoing major or minor surgical procedures).<sup>16</sup> Patients received bolus intravenous NovoSeven (either 35

micrograms per kg, N=15; or 90 micrograms per kg, N=14) prior to surgery, intra-operatively as required, then every 2 hours for the following 48 hours beginning at closure of the wound. Additional doses were administered every 2 to 6 hours up to an additional 3 days to maintain hemostasis. After a maximum of 5 days of double-blind treatment, therapy could be continued in an open-label manner if necessary (90 micrograms per kg NovoSeven every 2-6 hours) (Table 6). Efficacy was assessed during the intra-operative period, and post-operatively from the time of wound closure (Hour 0) through Day 5.

**Table 6: Dosing by Surgery Category**

	Major Surgery		Minor Surgery	
	35 µg/kg* (n = 5)	90 µg/kg (n = 6)	35 µg/kg (n = 10)	90 µg/kg (n = 8)
Days of dosing, median (range)	15 (2-26)	9.5 (8-17)	4 (3-6)	6 (3-13)
No. injections, median (range)	135 (11-186)	81 (71-128)	29.5 (24-44)	39.5 (26-98)
Median total dose, mg (range)	656 (31-839)	569 (107-698)	45.5 (14-171)	67 (31-122)

\* µg/kg = micrograms per kg body weight

Intraoperative hemostasis was achieved in 28/29 (97%) patients. Satisfactory hemostasis was achieved in 14/14 (100%) patients in the 90 mcg/kg dose group and 11/15 (73%) in the 35 mcg/kg dose group at 48 hours; satisfactory hemostasis was achieved in 13/14 (93%) in the 90 mcg/kg dose group and 11/15 (73%) in the 35 mcg/kg dose group at 5 days. Twenty-three patients successfully completed the entire study including 13/14 (93%) achieving successful hemostasis through study completion (up to day 26) in the 90 mcg/kg dose group.

Another open-label, randomized, parallel trial was conducted to compare the safety and efficacy of bolus intravenous (BI) injection (N=12) and continuous intravenous (CI) infusion (N=12) administration of NovoSeven in 23 hemophilia A or B patients with inhibitors and one patient with acquired hemophilia who were undergoing elective major surgery. Table 7 provides the overview of dosing by treatment group for BI and CI.

**Table 7: Dosing by Treatment Group**

	<b>Bolus Injection</b> <b>90 micrograms/kg</b> (n = 12) <sup>a</sup>	<b>Continuous Infusion</b> <b>50 micrograms/kg/h</b> (n = 12)
Days of dosing, median (range)	10 (4-15) <sup>b</sup>	10 (2-116)
No. bolus injections, median (range)	38 (36-42)	1.5 (0-7)
No. of additional bolus injections, median (range)	0 (0-3)	0 (0-4)
Mean total dose, mg	237.5	292.2

<sup>a</sup> Includes one patient with acquired hemophilia

<sup>b</sup> Includes dosing during the follow-up period after the 10-day study period.

Intraoperative hemostasis was reported as effective in all BI and CI treated patients. BI regimen was 100% effective through the first 24 hours, and was 92% effective at day 5. CI regimen was 83% effective through the first 24 hours, and was 83% effective at day 5. At the end of the study period (Post operative day 10 or discontinuation of therapy), hemostatic efficacy in the BI and CI arms was 9/12 (75%) and 10/12 (83%), respectively.

#### **14.2 Congenital Factor VII Deficiency**

Data were collected from the published literature, compassionate use trials and registries for 70 patients with Factor VII deficiency treated with NovoSeven for 124 bleeding episodes, surgeries, or prophylaxis regimens. Thirty-two of these patients were enrolled in emergency and compassionate use trials conducted by Novo Nordisk (43 non-surgical bleeding episodes, 26 surgeries); 35 were reported in the published literature (20 surgeries, 10 non-surgical bleeding episodes, 4 cases of caesarean section or vaginal birth, and 10 cases of long-term prophylaxis, and 1 case of on-demand therapy); and 3 were from a registry maintained by the Hemophilia and Thrombosis Research Society (9 bleeding episodes, 1 surgery). Dosing ranged from 6 to 98 micrograms per kg administered every 2-12 hours (except for prophylaxis, where doses were administered from 2 times per day up to 2 times per week). Patients were treated with an average of 1-10 doses. Treatment was effective (bleeding stopped or treatment was rated as effective by the physician) in 93% of episodes (90% for trial patients, 98% for published patients, 90% for HTRS registry patients).

#### **14.3 Acquired Hemophilia**

Data were collected from four studies in a compassionate use program conducted by Novo Nordisk and the Hemophilia and Thrombosis Research Society (HTRS) registry. The studies were not designed to select doses or compare first-line efficacy or efficacy when used after failure of other hemostatic agents (salvage

treatment). A total of 70 patients with acquired hemophilia were treated with NovoSeven for 113 bleeding episodes, surgeries, or traumatic injuries. Sixty-one of these patients were from the compassionate use program with 100 bleeding episodes (68 non-surgical and 32 surgical bleeding episodes) and 9 patients were from the HTRS registry with 13 bleeding episodes (8 non-surgical, 3 surgical and 2 episodes classified as other). Concomitant use of other hemostatic agents occurred in 29/70 (41%); 13 (19%) received more than one hemostatic agent. The most common hemostatic agents used were antifibrinolytics, Factor VIII and activated prothrombin complex concentrates.

The mean dose of NovoSeven administered was 90 micrograms per kg (range: 31 to 197 micrograms per kg); the mean number of injections per day was 6 (range: 1 to 10 injections per day). Overall efficacy (i.e., effective and partially effective outcomes) was 87/112 (78%); with 77/100 (77%) efficacy in the compassionate use programs and 10/12 (83%) efficacy in the HTRS registry. In the compassionate use programs, overall efficacy for the first-line treatment was 38/44 (86%) compared to 39/56 (70%) when used as salvage treatment (Table 8).

**Table 8: Efficacy by Dose Group, for Patients Receiving Doses Ranging from <61 to >90 micrograms/kg NovoSeven, Compassionate Use Programs and HTRS Registry**

Outcome <sup>a</sup>	NovoSeven Dose (micrograms/kg)							Total
	Un-known	<61	61-69	70-80	81-89	90	>90	
Effective N (%)	1 (33)	3 (75)	5 (63)	10 (63)	12 (57)	10 (67)	26 (58)	67
Partial N (%)	1 (33)	0 (0)	0 (0)	3 (19)	3 (14)	2 (13)	11 (24)	20
Ineffective N (%)	0 (0)	1 (25)	3 (38)	2 (13)	2 (10)	2 (13)	7 (16)	17
Unknown N (%)	1 (33)	0 (0)	0 (0)	1 (6)	4 (19)	1 (7)	1 (2)	8
No. of Bleeding Episodes <sup>c</sup>	3	4	8	16	21	15	45	112 <sup>b</sup>

<sup>a</sup> Outcome assessed at end of treatment, last observation carried forward.

<sup>b</sup> One patient in the HTRS registry was excluded from efficacy analysis since NovoSeven was used to maintain hemostasis after bleeding had been controlled.

<sup>c</sup> N (%) do not add up to 100 due to rounding.

#### 14.4 Glanzmann's Thrombasthenia

Data were collected from the Glanzmann's Thrombasthenia Registry (GTR), the Hemostasis and Thrombosis Research Society (HTRS) registry, and the published literature. The GTR was observational, and therefore not designed to select doses. The GTR captured data for 218 Glanzmann's thrombasthenia patients with 1073 bleeding and surgical events. An independent adjudication committee assessed clinical refractoriness and antibody status based upon historical data from investigators, patterns of treatment, and treatment responses when only platelets were used. Adjudicators defined clinical refractoriness as lack of platelet response. Patients with apparent response to platelets only were not considered refractory, even if coded as such by investigators. Antibody status included GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies. Efficacy was

evaluated on a two-point scale (clinical assessment of success or failure of treatment regimen as a whole, blinded and unblinded to investigator coded outcome) in 190 patients with 755 episodes requiring systemic hemostatic therapy (151 patients with 564 severe bleeding episodes, 90 patients with 192 surgeries, one episode was classified as both). Of these a total of 92 patients were treated with NovoSeven RT for 266 bleeding episodes and 77 patients treated for 160 surgical procedures. A large number of bleeding episodes were treated with NovoSeven RT alone (109/266 (41%) events).

The median dose of NovoSeven RT administered for bleeding episodes and surgical procedures was 90 micrograms per kg and the median interval between doses was 3 hours.

For all subjects, concomitant use of other hemostatic agents occurred in 157/266 (59%) bleeding episodes and 94/160 (59%) surgical procedures.

The majority of NovoSeven RT treated bleeding episodes were in pediatric patients (65%; children and adolescents, 0-16 yrs.).

Of the 266 bleeding episodes treated with NovoSeven RT, the most common types of bleeding episodes were: epistaxis (116, 43.6%), gum bleeding (48, 18.0%), menorrhagia (36, 13.5%), tooth/dental extraction related (29, 10.9%), and gastrointestinal (23, 8.6%).

Of the patients treated with NovoSeven RT for surgical procedures, 86% were adults (> 16 years). Major surgery was defined as any invasive operative procedure in which, body cavity was entered, mesenchymal barrier was crossed, facial plane was opened, organ was removed or normal anatomy was operatively altered. Minor surgery was defined as any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue were manipulated. Surgical procedures treated with NovoSeven RT included minor (134/160; 83.8%) and major (26/160, 16.3%) procedures. Dental procedures were most common (106, 66.3%), followed by endoscopy (12, 7.5%), nasal procedures (8, 5.0%), excision (7, 4.4%), GI surgery (7, 4.4%) and orthopedic procedures (6, 3.8%). Most surgeries were elective (147, 91.9%), with a few emergency (7, 4.4%) or unspecified (6).

Overall, treatment with NovoSeven RT was successful in 94.4% of bleeding episodes (Table 9) and 99.4% of surgical procedures (Table 10). Adjudicator-rated efficacy was consistent across treatment regimens, bleed and surgery types, age, and refractory/antibody status. Treatment with NovoSeven RT was successful in patients with clinical refractoriness with or without platelet-specific antibodies in 94.9% of bleeding episodes and 98.6% of surgical procedures. In patients without refractoriness or platelet-specific antibodies, treatment with NovoSeven RT was comparable to treatment with platelets.

**Table 9: Adjudicator Evaluation of Efficacy – Bleeding Episodes for GTR Data**

	No. of patients <sup>c</sup>	No. of episodes	Success	Failure	Insufficient data	No Consensus
All NovoSeven*	92	266	251 (94.4)	4 (1.5)	6 (2.3)	5 (1.9)
<b>By Treatment Regimen</b>						
NovoSeven only	44	109	101 (92.7)	2 (1.8)	4 (3.7)	2 (1.8)
NovoSeven ± Platelets ± Other hemostatic agents	69	157	150 (95.5)	2 (1.3)	2 (1.3)	3 (1.9)
<b>By Antibody/Refractory Group</b>						
Refractoriness ± Platelet-specific antibodies <sup>a,d</sup>	31	79	75 (94.9)	2 (2.5)	2 (2.5)	0 (0.0)
Platelet-specific-antibodies <sup>a,d</sup>	8	10	10 (100.0)	0 (0.0)	0 (0.0)	NA
Neither or unknown <sup>b,d</sup>	57	177	166 (93.8)	2 (1.1)	4 (2.3)	5 (2.8)

\*All treatment regimens that included treatment with NovoSeven

<sup>a</sup> includes GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies

<sup>b</sup> Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractory status unknown

<sup>c</sup> Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractory status

<sup>d</sup> Treatment was NovoSeven only for 26/79 episodes with refractoriness with or without antibodies, 2/10 episodes with platelet specific antibodies only, and 81/177 episodes with neither or unknown. The remainder received NovoSeven with platelets and/or antifibrinolytic agents.

**Table 10: Adjudicator Evaluation of Efficacy – Surgical Procedures for GTR Data**

Treatment group	No. of patients <sup>c</sup>	No. of procedures	Success	Insufficient data <sup>d</sup>
All NovoSeven*	77	160	159 (99.4)	1 (0.6)
By Treatment Regimen				
NovoSeven only	35	66	65 (98.5)	1 (1.5)
NovoSeven ± Platelets ± Other hemostatic agents	57	94	94 (100.0)	0 (0.0)
By Antibody/Refractory Group				
Refractoriness ± Platelet-specific antibodies <sup>a,e</sup>	33	70	69 (98.6)	1 (1.4)
Platelet-specific antibodies <sup>a,e</sup>	11	24	24 (100.0)	0 (0.0)
Neither or unknown <sup>b,e</sup>	36	66	66(100)	0 (0.0)

\*All treatment regimens that included treatment with NovoSeven

<sup>a</sup> includes GPIIb/IIIa, HLA, and unspecified platelet-specific antibodies

<sup>b</sup> Assumes no platelet-specific antibodies or refractoriness reported or antibody and refractory status unknown

<sup>c</sup> Patient numbers are not additive. Patients may have episodes with different treatment regimens and have more than one antibody/refractory status

<sup>d</sup> No reports of failure or lack of consensus was reported

<sup>e</sup> Treatment was NovoSeven only for 22/70 episodes with refractoriness with or without antibodies, 13/24 episodes with platelet specific antibodies only, and 31/66 episodes with neither or unknown. The remainder received NovoSeven with platelets and/or antifibrinolytic agents.

In HTRS, there were 7 patients that were treated with NovoSeven RT for 23 bleeding episodes. Concomitant hemostatic agents were administered for 11 episodes (antifibrinolytics in 10 episodes). Treatment was reported effective in 21 of 23 (91.3%) episodes. In the other 2 episodes, bleeding was reported as slowed or no improvement, however in neither episode was further treatment reported. There were no surgical procedures reported in the HTRS registry.

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

### *How Supplied*

NovoSeven RT, Coagulation Factor VIIa (Recombinant), is supplied as a room temperature stable, white, lyophilized powder in single-use vials, one vial per carton. The diluent for reconstitution of NovoSeven RT is a 10 mmol solution of L-histidine in water for injection and is supplied as a clear colorless solution, and referred to as the histidine diluent. The histidine diluent is provided in either a vial or pre-filled diluent syringe. The amount of rFVIIa in milligrams and in micrograms is stated on the label.

NovoSeven RT package containing 1 vial of NovoSeven RT powder and 1 vial of histidine diluent:

Presentation	Carton NDC Number	Components
1 mg per vial (1000 micrograms/vial)	NDC 0169 7010 01	<ul style="list-style-type: none"><li>• NovoSeven RT in a single-use vial [NDC 0169-7010-01]</li><li>• Histidine diluent in vial, 1.1 mL</li></ul>
2 mg per vial (2000 micrograms/vial)	NDC 0169 7020 01	<ul style="list-style-type: none"><li>• NovoSeven RT in a single-use vial [NDC 0169-7020-01]</li><li>• Histidine diluent in vial, 2.1 mL</li></ul>
5 mg per vial (5000 micrograms/vial)	NDC 0169 7050 01	<ul style="list-style-type: none"><li>• NovoSeven RT in a single-use vial [NDC 0169-7050-01]</li><li>• Histidine diluent in vial, 5.2 mL</li></ul>
8 mg per vial (8000 micrograms/vial)	NDC 0169 7040 01	<ul style="list-style-type: none"><li>• NovoSeven RT in a single-use vial [NDC 0169-7040-01]</li><li>• Histidine diluent in vial, 8.1 mL</li></ul>

NovoSeven RT with MixPro<sup>®</sup> package containing 1 vial of NovoSeven RT powder and 1 pre-filled histidine diluent syringe with sterile vial adapter which serves as an alternative needleless reconstitution system:

Presentation	Carton NDC Number	Components
1 mg per vial (1000 micrograms/vial)	NDC 0169 7201 01	<ul style="list-style-type: none"> <li>• NovoSeven RT in a single-use vial [NDC 0169-7211-11]</li> <li>• Pre-filled histidine diluent in syringe, 1 mL [NDC 0169-7011-98]</li> <li>• Vial adapter</li> </ul>
2 mg per vial (2000 micrograms/vial)	NDC 0169 7202 01	<ul style="list-style-type: none"> <li>• NovoSeven RT in a single-use vial [NDC 0169-7212-11]</li> <li>• Pre-filled histidine diluent in syringe, 2 mL [NDC 0169-7012-98]</li> <li>• Vial adapter</li> </ul>
5 mg per vial (5000 micrograms/vial)	NDC 0169 7205 01	<ul style="list-style-type: none"> <li>• NovoSeven RT in a single-use vial [NDC 0169-7215-11]</li> <li>• Pre-filled histidine diluent in syringe, 5 mL [NDC 0169-7015-98]</li> <li>• Vial adapter</li> </ul>
8 mg per vial (8000 micrograms/vial)	NDC 0169 7208 01	<ul style="list-style-type: none"> <li>• NovoSeven RT in a single-use vial [NDC 0169-7218-11]</li> <li>• Pre-filled histidine diluent in syringe, 8 mL [NDC 0169-7018-98]</li> <li>• Vial adapter</li> </ul>

The NovoSeven RT and histidine diluent vials are made of glass closed with a chlorobutyl rubber stopper not made with natural rubber latex, and covered with an aluminum cap. The pre-filled diluent syringes are made of glass, with a siliconised bromobutyl rubber plunger not made with natural rubber latex. The closed vials and pre-filled diluent syringes are equipped with a tamper-evident snap-off cap which is made of polypropylene. A vial adapter with 25 micrometer filter is provided with the pre-filled diluent syringe.

#### *Storage and Handling*

Prior to reconstitution, store NovoSeven RT powder and histidine diluent between 2-25°C (36-77°F). Do not freeze. Store protected from light. Do not use past the expiration date.

After reconstitution, store NovoSeven RT either at room temperature or refrigerated for up to 3 hours. Do not freeze reconstituted NovoSeven RT or store in syringes.

**17 PATIENT COUNSELING INFORMATION**  
**See FDA-approved patient labeling (Instructions for Use)**

- Inform patients receiving NovoSeven RT the benefits and risks associated with treatment.
- Advise patients about the early signs of hypersensitivity reactions, including hives, urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
- Advise patients about the signs of thrombosis, including new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness or speech.
- Advise patients to immediately seek medical help if any of the above signs or symptoms occur.

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NovoSeven<sup>®</sup> RT is covered by US Patent No. 8,299,029, and other patents pending.

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